National Cancer Institute

Cancer Risks in Children Undergoing Radiotherapy

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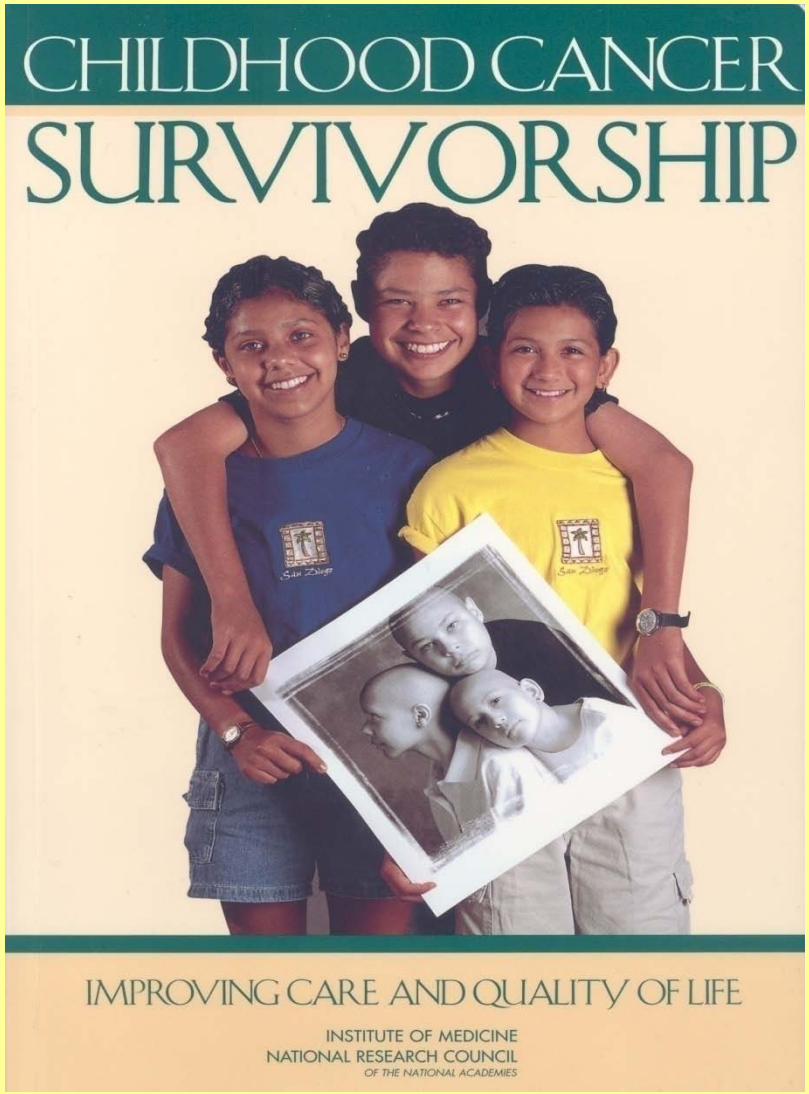
National Institutes of Health

Late Effects After Childhood Cancer



Why Study Second Cancers?

- Understanding risks can inform patient care:
  - Identification of persons at high risk
  - Surveillance, screening
  - Interventions
  - Risk-adjusted treatment
  - Modifications of treatment

- Insights into cancer biology & radiobiology

Second Cancers Following Childhood vs. Adult First Cancers

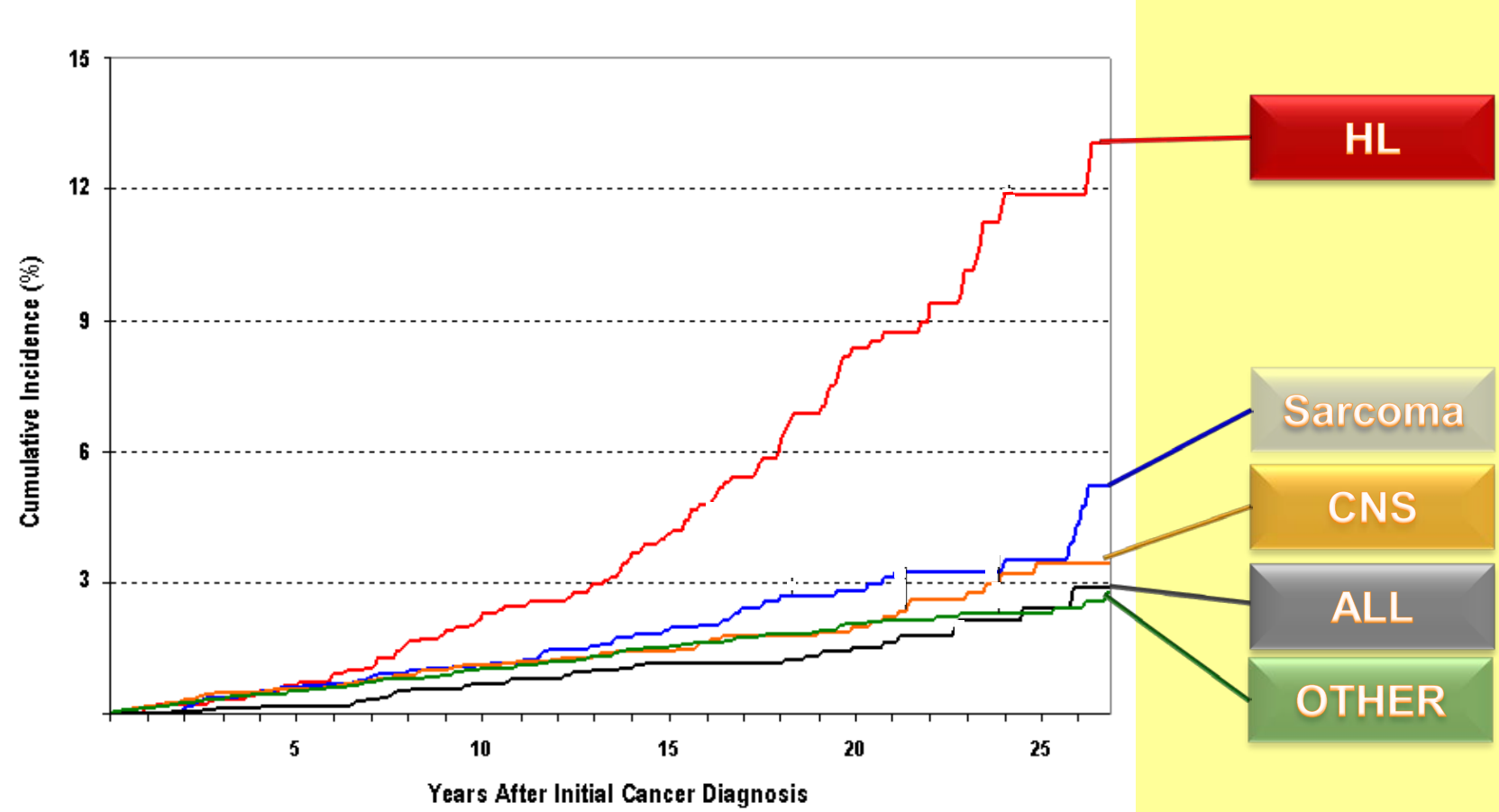
- Different types of 1st cancer relative to adults
- Higher survival, longer expected remaining lifetimes → longer period for adverse effects to be expressed
- Possible greater sensitivity to effects of treatment at early developmental stages
- Children have had lesser opportunity to have experienced confounding environmental exposures → effects of treatment & genetic susceptibility can be evaluated more clearly

Incidence of Childhood Cancers (SEER)

Cancer type	Annual Rate per Million
Leukemia	37
Brain/CNS	25
Lymphoma	24
Carcinomas	14
Germ cell cancers	10
Soft tissue sarcoma	11
Bone sarcoma	9

Ries et al. (1999)

Disproportionate Share of 2nd Cancers Occur Among Persons Whose 1st Cancer Was Hodgkin Lymphoma (HL)



Inskip & Curtis, *Int J Cancer* (2007)

Relative Risk of Subsequent Leukemia (ANLL), By Initial Treatment for Childhood Cancer

Initial Treatment	Cases	RR*	95% CI
No radiotherapy	21	1.0	reference
Any radiotherapy	13	0.8	0.4 – 1.7
No chemotherapy	116	1.0	reference
Any chemotherapy	157	7.3	2.1 – 25.8

* Based on Poisson regression using SEER data for one-year survivors

Inskip & Curtis, *Int J Cancer* (2007)

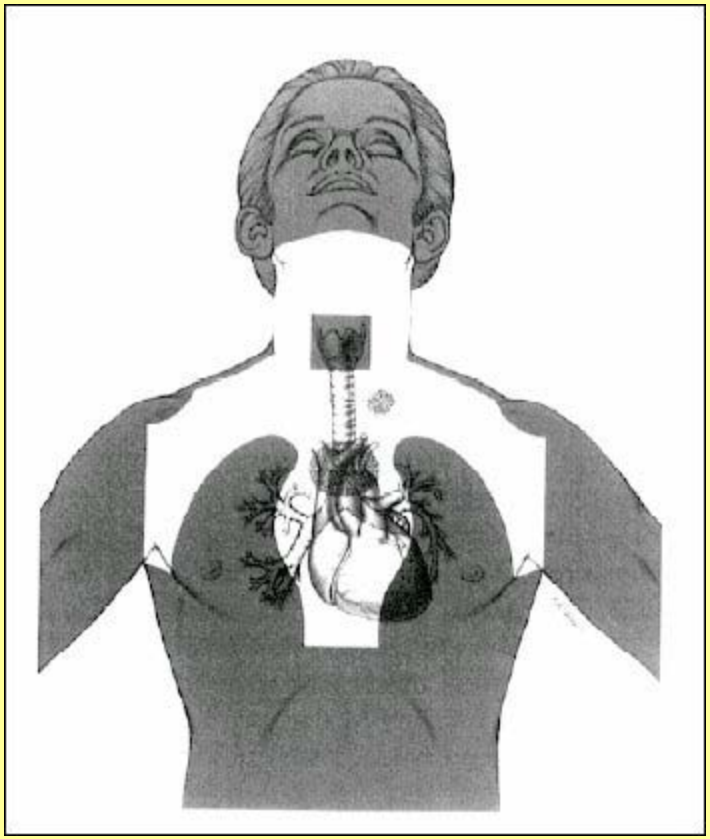
Relative Risk of Subsequent Solid Cancers, By Initial Treatment for Childhood Cancer

Initial Treatment	Cases	RR*	95% CI
No radiotherapy	98	1.0	reference
Any radiotherapy	175	1.9	1.5 – 2.5
No chemotherapy	116	1.0	reference
Any chemotherapy	157	1.4	1.1 – 1.9

* Based on Poisson regression using SEER data for five-year survivors

Inskip & Curtis, *Int J Cancer* (2007)

Mantle Field Radiotherapy for Hodgkin Lymphoma



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Ries et al. (1999)

Need for Multicenter Studies

- Children's Oncology Group (COG)
  - consortium of hospitals involved in clinical trials
  - primary aim is to study efficacy of treatment and short-term complications
- Childhood Cancer Survivor Study (CCSS)
  - designed to study longer term effects of childhood cancer and its treatment

Childhood Cancer Survivor Study (CCSS)

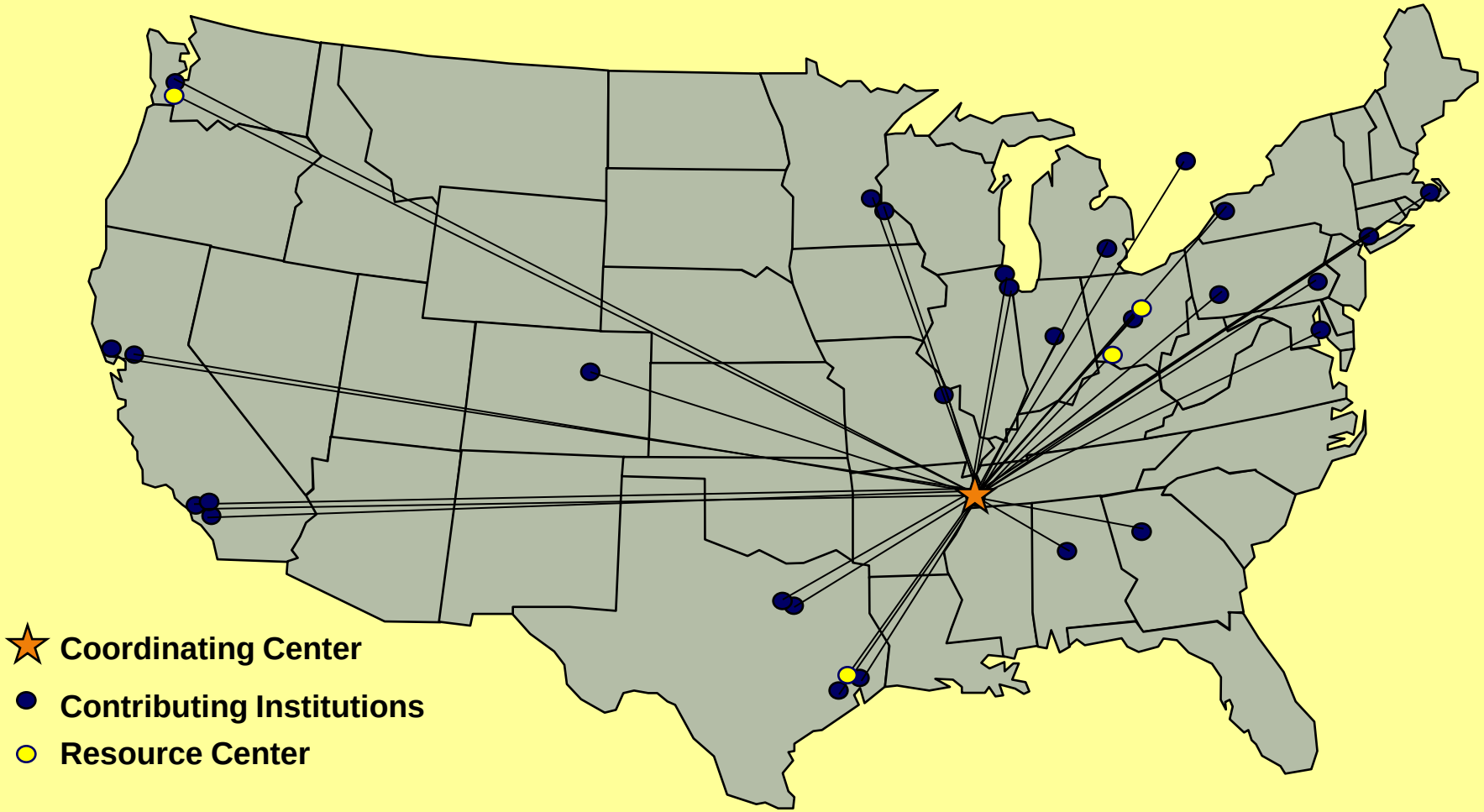
- Multi-center cohort study of 14,358 five-year survivors of childhood cancer diagnosed 1970-86
- Detailed information on treatment from medical records
- Long-term follow-up
- Baseline questionnaire + resurveys every 2-3 y
- Sibling cohort for comparison (N=3,899)
- Biological specimens
- Developed as resource for scientific community
- See http://ccss.stjude.org for more information

Robison *et al.*, *Med Pediatr Oncol* (2002)

CCSS
An NCI-Funded Resource

Childhood Cancer Survivor Study
Participating Centers

St. Jude Children's Research Hospital
ALSAC • Danny Thomas, Founder
Finding cures. Saving children.



Cause-specific Mortality (CCSS)

				RT vs. No RT	
Cause of Death	Deaths[#]	SMR*	(95% CI)	RR[@]	(95% CI)
Second cancer	470	15.2	(13.9-16.6)	2.9	(2.1-4.2)
Cardiac causes	142	7.0	(5.9-8.2)	3.3	(2.0-5.5)
Pulmonary causes	67	8.8	(6.8-11.2)	1.4	(0.7-2.9)

[#] Through 2002

* Standardized mortality ratio, based on general population comparisons

[@] Relative risk based on internal comparisons

Mertens et al., *JNCI* (2009)

Examples of Studies of Second Cancers in the CCSS Cohort

Thyroid

Brain/CNS

Breast

Themes

- Radiation-related risk does not always increase monotonically with dose
- Strong effect of age at exposure for some solid cancers
- Different histologic types of 2nd cancer within an organ can exhibit different associations with treatment and other factors
- Indirect effects of radiation on 2nd cancer risk

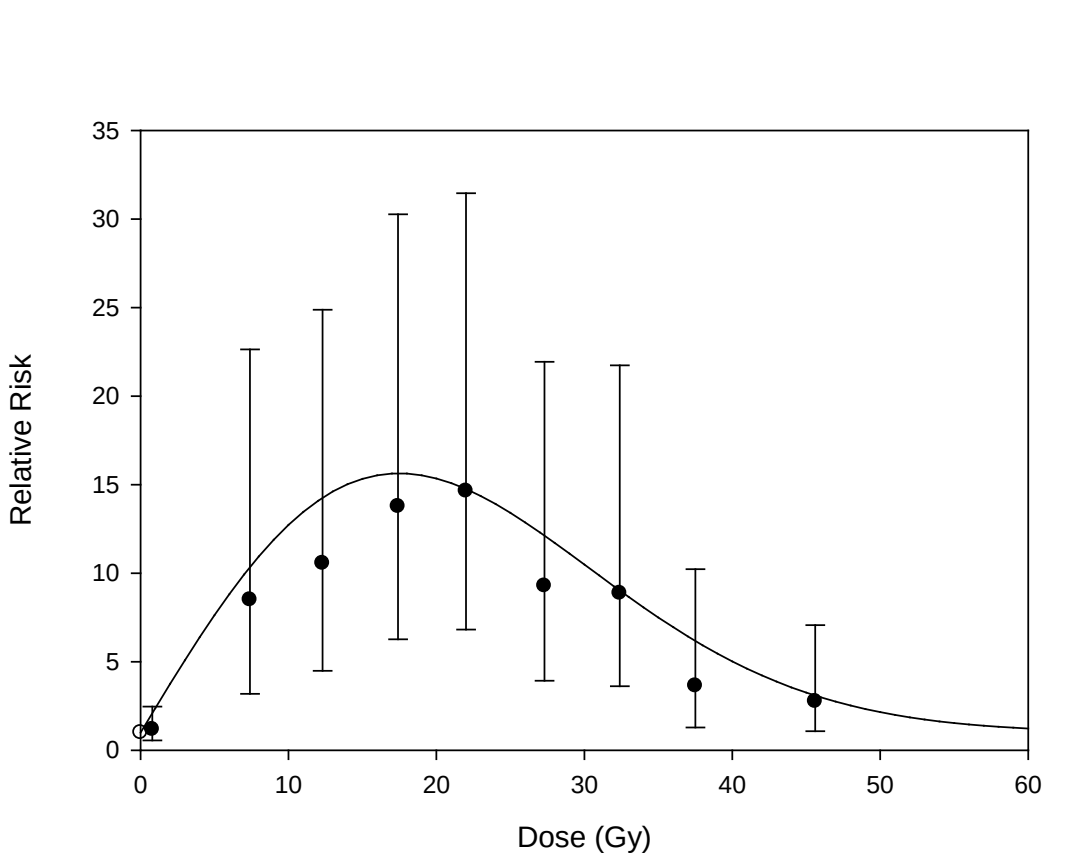
Thyroid Cancer after Childhood Cancer

- Study conducted within the CCSS
  - 119 cases of 2nd primary thyroid cancer
  - 33% with Hodgkin lymphoma as 1st cancer

- Thyroid doses estimated for entire cohort

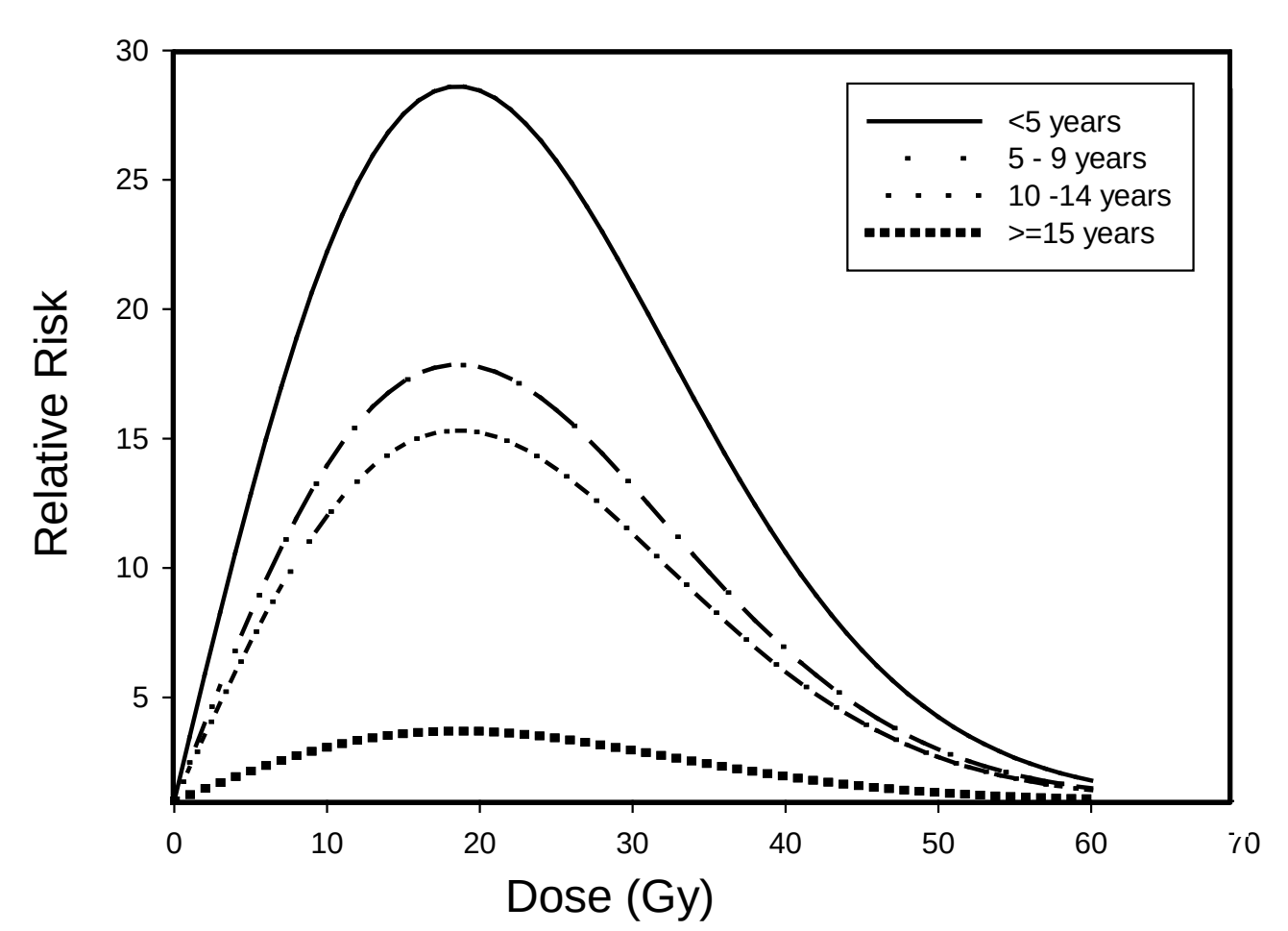
Bhatti et al., *Radiat Res (*2011)

Thyroid Cancer Risk By Radiation Dose



Bhatti et al., *Radiat Res* (2011)

Relative Risk of Thyroid Cancer by Dose & Age at Exposure



Bhatti et al. *Radiat Res* (2011)

Risk of Thyroid Cancer by Dose of Alkylating Agents and Dose of Radiation

	Radiation Dose (Gy)			
	≤ 20			
Alkylating Agent Score	0 RR	0-5 RR	0-20 RR	>20 RR
Not exposed	1.0*	1.0*	1.0*	1.0*
Low/medium	1.5	2.5	2.2	1.0
Highly exposed	10.1	5.5	2.7	0.9
P (trend)	0.07	0.02	0.03	>0.5

* Reference category

Veiga *et al*., submitted

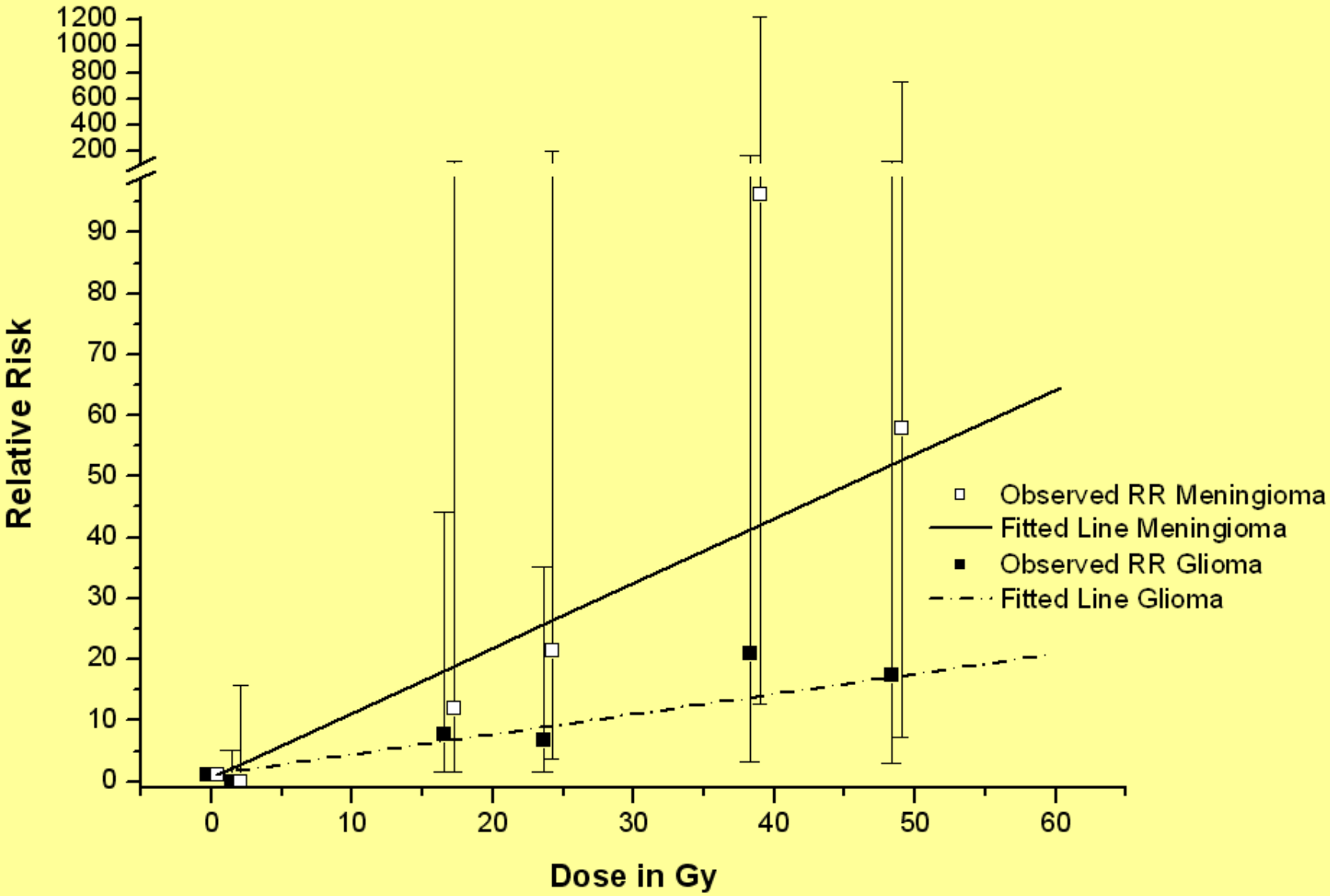
Brain Tumors Following Childhood Cancer in the CCSS

	Cases*	Controls	OR	95% CI
Chemotherapy				
No	25	78	1.0	reference
Yes	87	352	0.8	0.3 – 2.0
Radiotherapy				
No	5	120	1.0	reference
Yes	110	320	7.1	2.8 - 18

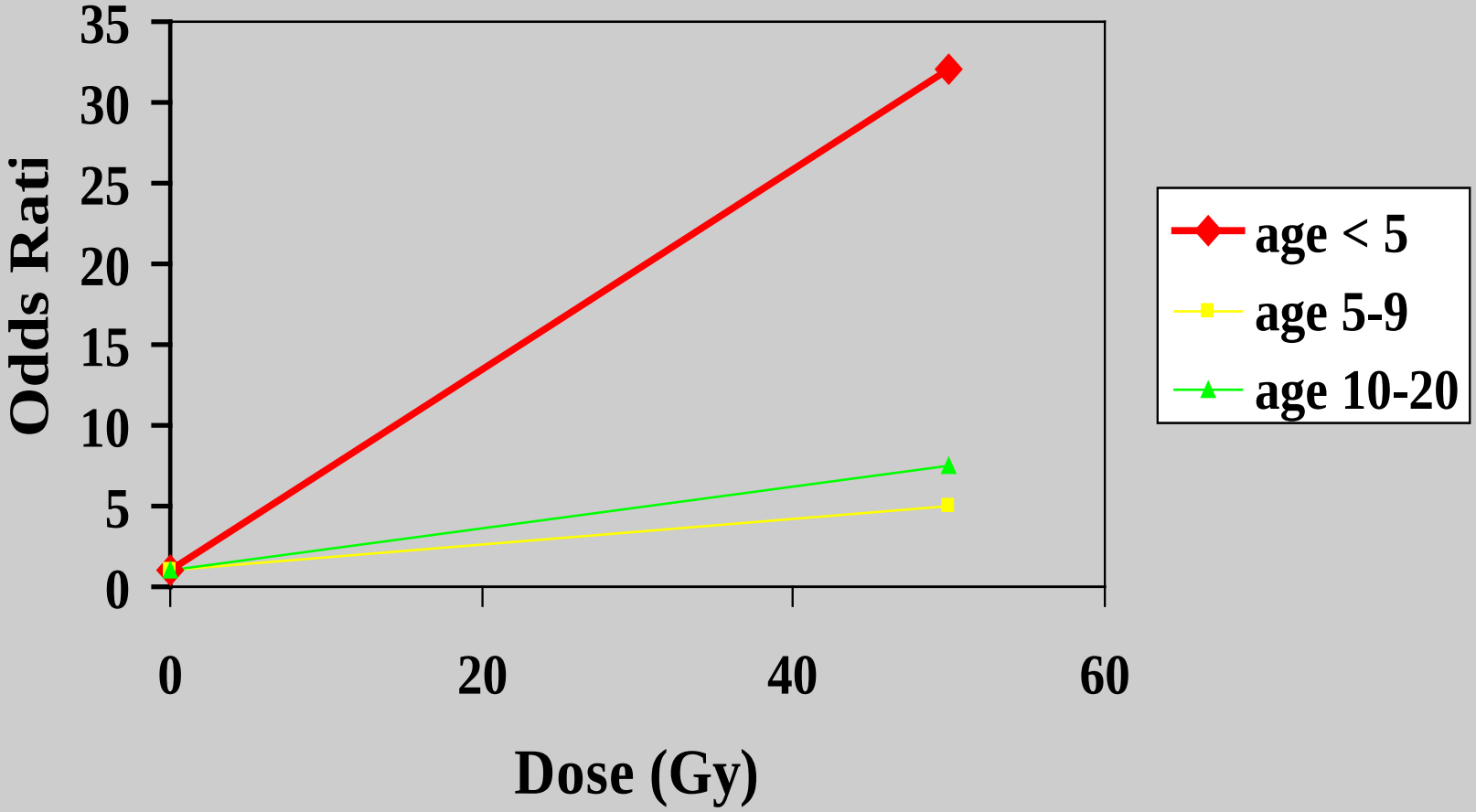
* Includes 40 gliomas and 66 meningiomas

Neglia et al. (*J Nat Cancer Inst 2006)*

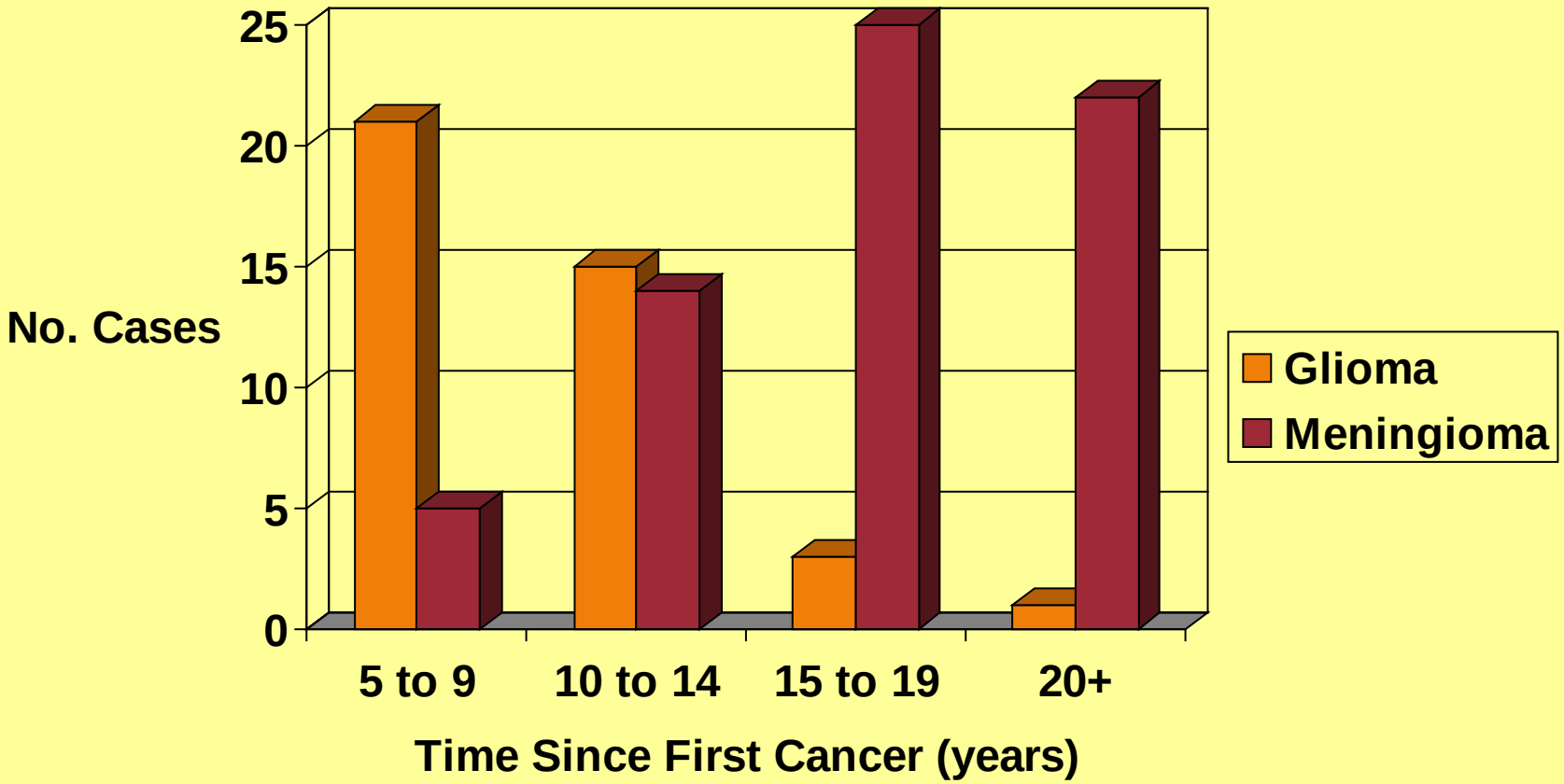
Brain Tumors Following Childhood Cancer



Risk of Glioma Following Radiotherapy for Childhood Cancer, By Age at 1st Cancer



Second Primary Brain Tumors After Childhood Cancer



Second Glioma vs. 2nd Meningioma

- Steeper dose-response for meningioma
- Glioma, but not meningioma, shows inverse association of risk with age at irradiation
- 2nd gliomas appear early, whereas 2nd meningiomas are more delayed and sustained

Comparison of CCSS & Tinea Capitis Study Results for CNS Tumors

	Radiotherapy for:	
	Childhood Cancer	Tinea capitis*
ERR/Gy:		
glioma	0.33 (CI: 0.07-1.71)	1.98 (CI: 0.73-4.69)
meningioma	1.06 (CI:0.21-8.15)	4.63 (CI: 2.43-9.12)
Association w/age at exposure?		
glioma	yes	yes
meningioma	no	no

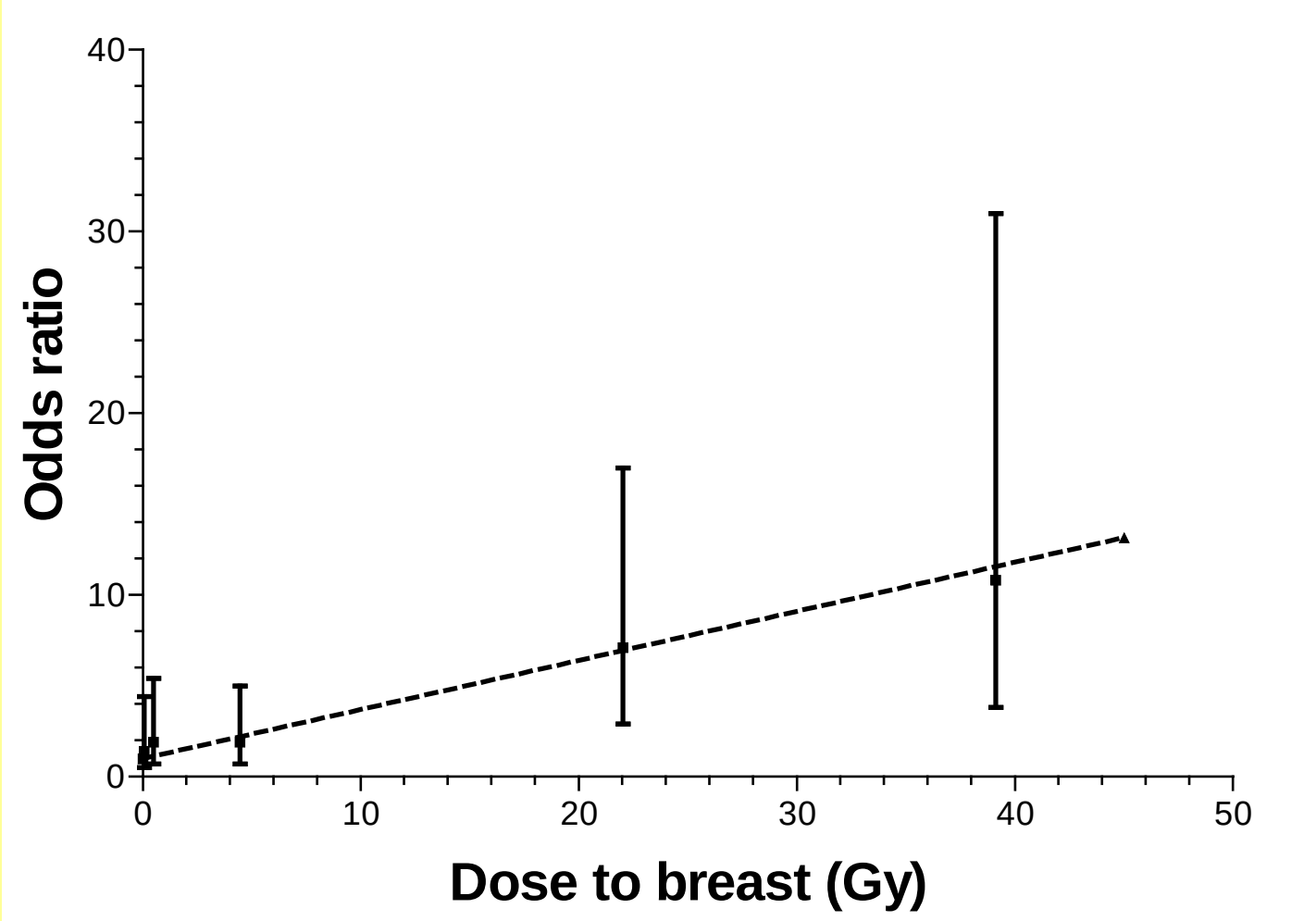
*Sadetzki et al. *Radiat Res* (2005)

Breast Cancer after Childhood Cancer

- Case-control study
- 120 cases
  - 65% of cases with Hodgkin lymphoma as 1st cancer (versus 13% in total cohort)
- Radiation dose to breast cancer site and to ovaries estimated by medical physicists

Inskip *et al.*, *J Clin Oncol* (2009)

Breast Cancer Risk by Radiation Dose



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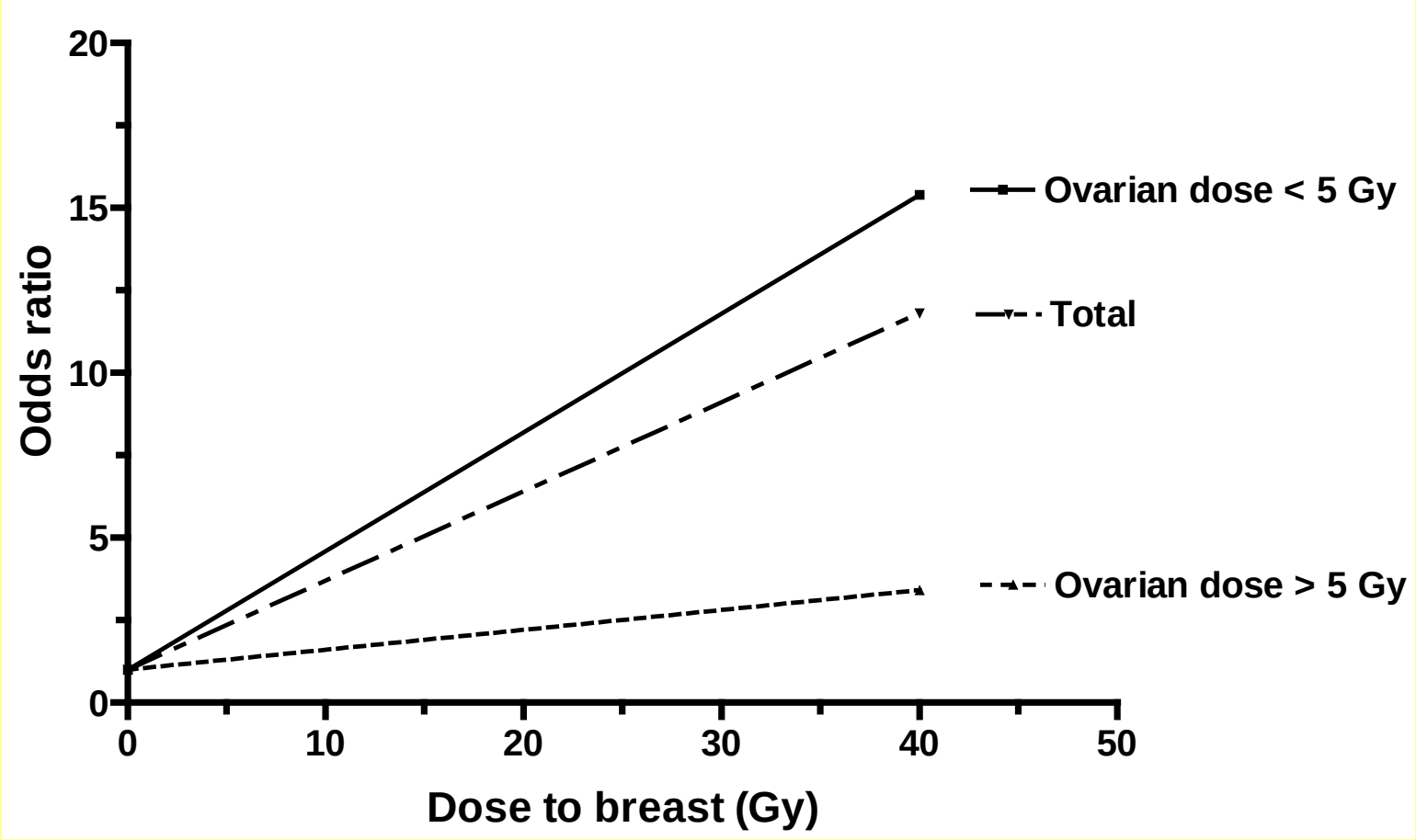

Inskip *et al.*, *J Clin Oncol* (2009)

Other Cancers Linked to Radiotherapy in the CCSS

- Basal cell carcinoma of the skin
- Bone & soft tissue sarcoma
- Carcinoma of salivary glands
- Carcinoma of colon*
- Carcinoma of stomach*
- Acute non-lymphocytic leukemia

* Numbers most of the common adult cancers still small; will be important to evaluate in the future

Changes in Radiotherapy Over Time

- Reduction in use of radiotherapy for most childhood cancers + lower doses
- Mantle radiotherapy for Hodgkin lymphoma (HL) largely discontinued in the 1990s
- Current practice for HL is to use involved fields rather than extended fields
  - Smaller volume of irradiated tissue
  - Lower administered dose per field

Mean Organ Doses By Treatment Plan for Hodgkin Lymphoma

	Integral Dose (Gy)			
	Breast	Thyroid	Lung	Heart
35 Gy Mantle	9.0	34.4	14.7	24.2
35 Gy IFRT	3.2	34.6	11.2	17.2
20 Gy IFRT	1.8	19.7	6.4	9.9

IFRT= Involved field radiotherapy

N = 41 patients

Koh et al. *Radiat Oncol* (2007)

Breast Cancer Risk in Female Survivors of Hodgkin's Lymphoma: Lower Risk After Smaller Radiation Volumes

Marie L. De Bruin, Judith Sparidans, Mars B. van't Veer, Evert M. Noordijk, Marieke W.J. Louwman, Josée M. Zijlstra, Hendrik van den Berg, Nicola S. Russell, Annegien Broeks, Margreet H.A. Baaijens, Berthe M.P. Aleman, and Flora E. van Leeuwen

Summary/Conclusions

- Risk of second cancers highest in survivors who received radiotherapy to chest
- Risk is dose-dependent and excess appears at young age
- Risk does not always increase monotonically with dose
- Patterns of radiation-response can vary for tissues within an organ
- Irradiation of distant organs can influence outcome in organ of interest (indirect effects)
- Trend towards smaller fields and lower doses may lower risk of 2nd cancers in the future

ADDENDUM

Pediatric Radiotherapy for Benign Conditions

- Tinea capitis (ringworm of scalp)
- Skin hemangiomas
- Enlarged thymus